In recent onset RA excess mortality is not related to disease severity

The mortality associated with rheumatoid arthritis (RA) has been extensively studied over the past 50 years. Many studies have shown that patients with RA have higher mortality rates than those of the general population. Hospital based cohorts of patients with RA tend to have higher standardised mortality rates than RA cohorts derived from the community. This suggests that the excess mortality in RA is related to disease severity.

Most studies of mortality in RA have been carried out in cohorts of patients with established RA. However, more recently, there have been a number of studies of the mortality of inception cohorts of patients with RA. Two studies of RA inception cohorts with disease onset in the 1980s, recruited from hospital settings, failed to find any increase in mortality during the early years of follow up. By contrast, three other studies of inception cohorts, identified from the community or primary care during an equivalent period of time, showed continuing greater mortality in women with RA even in the early years of the disease.

In this issue of the Annals of the Rheumatic Diseases investigators of the Iowa Women’s Health Study report that mortality is increased in women with older onset RA during the early years of the disease (relative risk (RR) 1.52 (95% CI 1.03 to 2.20)). Women in this study were recruited from the list of holders of driver’s licences and developed RA after 1986. Data from the Mayo clinic also show that patients with recent onset RA, identified from the Rochester community, still have a moderate increase in mortality in comparison with the general population (standardised mortality rate (SMR) 1.27 (95% CI 1.13 to 1.41)). This excess mortality was observed over four decades despite a fall in RA incidence during the same time period. Kaplan-Meier survival curves were nearly identical for each of the four decades of incident RA. Patients with seropositive disease on the Norfolk Arthritis Register (who are recruited from primary care) also show an excess mortality from some causes.

In an effort to determine the mortality associated with RA, investigators of the Iowa Women’s Health Study report that recent onset RA is associated with an excess mortality in a community but not in a hospital setting. What might be the explanation for this?

**CARDIOVASCULAR DISEASE**

It seems that being rheumatoid factor (RF) positive, early in the course of arthritis, is a prognostic marker for premature mortality. The reasons for this are not clear but may reflect an increased inflammatory disease burden. In the Iowa Women’s Health Study mortality was significantly increased in those women who were seropositive for RF (RR 1.90 (95% CI 1.24 to 2.92)). This almost twofold increase in mortality in seropositive elderly women is similar to that seen in other studies.

Rheumatoid factor positivity in early RA is a marker for premature mortality

Cardiovascular diseases (CVD) are responsible for 40–50% of mortality in the general and rheumatoid populations. In the Iowa Women’s Health Study a moderate but non-significant increase in cardiovascular mortality (RR 1.46 (95% CI 0.76 to 2.81)) was seen in women with early RA. Cardiovascular mortality was significantly increased in seropositive women with inflammatory polyarthritis registered with the Norfolk Arthritis Register (NOAR) after 1990. Female patients with baseline seropositive disease had twice the expected CVD mortality compared with the general population (SMR 2.02 (95% CI 1.15 to 3.28)). Thus RF positive disease, as well as being associated with increased all-cause mortality, may also influence cause-specific mortality.

**INFECTIONS**

Other studies of mortality in RA cohorts have found that deaths from infections are increased. Excess mortality from infection seems to rise with increasing duration of arthritis. In the Iowa Women’s Health Study, despite a relatively short duration of RA, there was a trend towards increased deaths from infectious causes.

**SMOKING**

One might expect that smoking would strongly predict cardiovascular mortality and infectious respiratory deaths in RA. We know that a history of cigarette smoking is associated with increased risk of mortality and CVD in the general population. It also is associated with RF production in RA and is recognised to be a risk factor for RA. Wällberg-Jonsson et al did not find that smoking predicted CVD events or mortality in their study of seropositive patients with RA and smoking did not predict mortality in NOAR. It seems unlikely that the increased mortality in RA is simply due to the confounding effects of smoking. There does appear to be a complicated relationship between smoking, RF, and mortality in RA.

**INFLAMMATORY DISEASE**

The presence of RF probably reflects a greater inflammatory disease burden. We know that inflammation is important in predicting mortality in the general population and in the elderly female population. It is also important in predicting mortality in patients with RA. It seems likely that women with RA have increased mortality because of their excess inflammatory disease burden, which may promote atherosclerosis.

**DRUG TREATMENT**

As already mentioned, mortality was not increased in a Dutch, hospital based, inception cohort of patients with RA and this might be the consequence of aggressive use of disease modifying antirheumatic drugs (DMARDs). During the first year 91% of these patients with RA were treated with DMARDs. Furthermore, data from Wirchita suggest that methotrexate treatment in RA is associated with an improved life expectancy. This improvement in mortality was largely due to a reduction in cardiovascular deaths. It may be that early effective disease suppression leads to an improved life expectancy in RA.

**THE CLINICAL PICTURE**

It seems that the clinical picture of RA has changed over recent decades. There is evidence that the incidence and prevalence of RA are falling. This appears to be more marked in women, possibly owing to a protective effect of the oral contraceptive pill. There is also a suggestion that RA has become a less severe disease over time. However, it is
difficult to know whether this improvement in disease outcome is in response to a change in the nature of the disease or changes in the way it is treated. One might expect mortality rates to decrease if the natural history of RA has become less severe over more recent years.

These recent mortality papers suggest that those patients with RA who are referred to hospital and treated early do indeed have an improved life expectancy. Those who are referred late or are managed in the community, even though they have inherently milder disease, continue to have an adverse outcome, particularly from cardiovascular disease.


References